REMARKS

Claims 1-3 and 15 have been canceled without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the canceled claims in this or any other patent application.

Applicants have amended Claims 4-12 and 14 to delete reference to the Figures. Claims 6, 9, 10 and 14 are amended to no recite particular amino acids. Claims 4 and 5 are amended to include the limitation "wherein said isolated nucleic acid encodes a protein that stimulates the release of TNF-α in blood." Applicants have amended Claim 4 to be in independent form, and have amended Claims 5 and 17 to depend from Claim 4. Claim 14 is amended to include "or a complement thereof" to elements (a)-(g), to specify the conditions under which hybridization occurs, and to add the following text "wherein said isolated nucleic acid molecule is suitable for use as a PCR primer, or probe; and wherein said isolated nucleic acid is at least about 20 nucleotides in length." Claim 16 is amended to read "at least about 50 nucleotides in length." Claim 19 is amended to further indicate that the claimed host cells are "isolated." New Claims 21-31 have been added.

Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. Support for the amendments to Claims 4-5 can be found, for example, in Example 17 beginning at paragraph [0526]. Support for the amendments to Claims 6, 9, 10 and 14 can be found, for example, at Figure 80 and at paragraphs [0011] and [0017]. Support for the amendments to Claim 14 can be found, for example, at paragraphs [0012], [0227], [0317], and [0327] of the specification. Support for the amendment to Claim 16 and new Claims 21-25 can be found, for example, at paragraph [0012]. Support for new Claims 26-31 can be found, for example, in the claims as originally filed, and paragraphs [0227] and [0317].

Claims 4-14 and 16-31 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed May 18, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Priority Determination:

The PTO has stated that because the cited priority documents do not meet the requirements of 35 U.S.C. § 112, first paragraph, priority under 35 U.S.C. § 120 is set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/04342 filed 2/18/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/099792 filed 9/10/1998.

Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility, and Applicants are therefore entitled to the benefit of these earlier applications. The sequences of SEQ ID NOs: 79 and 80 and homologies of these sequences to known genes and gene families were first disclosed in US Provisional Application 60/099792 filed 9/10/1998 as SEQ ID NOs: 1 and 2, in Figures 1 and 2. The data in Example 17 (Identification of PRO Polypeptides That Stimulate TNF-α Release In Human Blood (Assay 128)), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 92, line 25, through page 93, line 1.

Rejections Under 35 U.S.C. §101

Claims 1-20 are rejected on the assertion that they are not supported by a specific, substantial and credible asserted utility or a well established utility. Specifically, the PTO asserts that the disclosure that PRO1356 gave positive results in the assay testing stimulation of TNF-α release in human blood is not substantial and specific. First, the PTO states that the specification does not provide a substantial utility because the specification does not provide statistical significance of the data, the number of samples tested, and information that would lead one skilled in the art to conclude that the results were repeatable. The PTO also cites several references to support the assertion that releasing TNF-α in blood would not provide a specific or substantial utility because TNF-α has undesirable physiological effects. Finally, the PTO asserts that the claimed nucleic acids lack utility because the specification does not teach how the claimed nucleic acids can be administered, how to handle side effects, and how to have a particular therapeutic benefit.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing*

a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than

not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The M.P.E.P. states that "Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. § 2107.01, part III (8th ed. 2004) (emphasis added). As the Court of Customs and Patent Appeals held in *Nelson v. Bowler*:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. *Nelson v. Bowler*, 626 F.2d 853, 856, (CCPA 1980) (emphasis added).

In *Nelson v. Bowler*, Nelson had developed and claimed a class of synthetic prostaglandins. At the time of the application, naturally occurring prostaglandins had a recognized value in pharmacology. To support his asserted utility, Nelson's application included test results demonstrating the bioactivity of his synthetic prostaglandins relative to the bioactivity of the natural prostaglandins. The court concluded that Nelson had satisfied the practical utility requirement in identifying the synthetic prostaglandins as pharmacologically active compounds,

rejecting arguments that attacked the evidentiary basis for Nelson's assertions that the compounds were pharmacologically active. *See* M.P.E.P. § 2107.01, part III (8th ed. 2004).

Similarly, in *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

Like the present case, the *Fujikawa* case was in the context of utility for pharmaceutical compounds, and thus the same standard of utility applies – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful to regulate the stimulation of the release of TNF-α.

Substantial Utility

Applicants first address the PTO's arguments that the data in Example 17 is insufficient to establish utility for the claimed nucleic acids because the specification fails to disclose sufficient information.

Regarding Example 17, the PTO states, "[t]here is no statement as to the statistical significance of the data. The number of samples tested with the PRO 1356 polypeptide is not disclosed. There is no information to allow the skilled artisan to conclude that the result in the specification is generally repeatable." Office Action at 2-3. Thus, the PTO appears to take the position that additional information, beyond the disclosure and asserted utility provided in the specification, for example, at Example 17, must have been provided in order for Applicants to establish a utility for the claimed nucleic acids and the encoded polypeptide.

Applicants submit that the PTO's position that the specification must have provided additional evidence in order to establish the utility of the claimed nucleic acids and encoded polypeptide is beyond that required to establish a utility for claimed subject matter. First, Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. See *In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); M.P.E.P. §2107.02 (III). Requests for additional

evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963); M.P.E.P. §2107.02 (V). Second, the PTO does not appear to question that release of TNF-α in blood was observed, but instead, the PTO takes the position that Applicants' specification must have provided additional details to establish the statistical significance of the data. Statistical certainty is not the proper standard for establishing utility. Instead, evidence will be sufficient if the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004).

The TNF-α release assay in the specification, Example 17, shows that blood samples treated with the PRO1356 polypeptide had higher amounts of TNF-α as compared to negative control samples. Identification of the TNF-α-releasing activity of the PRO1356 polypeptide renders the polypeptide and the encoding nucleic acid useful, as discussed below. Any requirement of additional data to demonstrate utility is not concordant with the proper standard for establishing utility.

Notwithstanding the presumption of utility that should be accorded to Applicants' claimed nucleic acids, Applicants submit herewith the declaration of Paul Godowski (attached as Exhibit 1), which was originally submitted in co-pending, co-owned patent application Serial No. 10/063,664. Dr. Godowski, an expert in the field, was responsible for performing the experiments reported in Example 17. In paragraph 5 of his declaration, Dr. Godowski states that the results reported in Example 17 are reliable and reproducible and that PRO1356 stimulated the release of at least 50-fold more TNF-α than compared to the control. He also states that this constitutes "a significant amount of TNF-α, and because more than a trace amount of TNF-α was released, the PRO polypeptides reported as positive are useful" as described in detail in the remainder of his declaration. *Exhibit 1 at paragraph 5.*

Applicants next turn to the PTO's argument that TNF-α release in the bloodstream would not provide a specific and substantial utility. The PTO cites Halle *et al.* (Exercise Immunol. Rev. 4:77, 1998) and Tsimberdou *et al.* (Expert Rev. Anticancer Ther. 2:277, 2002) as supporting the assertion that TNF-α release can have undesirable physiological effects. Applicants submit that the identification of possible undesirable physiological effects of a compound does not preclude the ability of the compound to also have desirable physiological effects, as is the case, for

example, with chemotherapeutic compounds. Further, the M.P.E.P. states that "Courts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. § 2107.01, part III (8th ed. 2004) (emphasis added). In addition, the Courts have held that "the test results need not absolutely prove that the compound is pharmacologically active. All that is required is that the tests be '*reasonably* indicative of the desired [pharmacological] response.'" *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, italics in original). Clearly, the stimulation of TNF-α release meets the test of "mere identification of a pharmacological activity" set forth in the M.P.E.P.

In addition, as is attested in the declaration of Paul Godowski, as of 1995 and earlier, it was known that enhanced TNF-α levels are beneficial in treating certain conditions, such as cancer and viral infection, and in reducing the deleterious effects of ionizing radiation. As attested in the accompanying Declaration, prior to the earliest priority date of the instant application, references described the therapeutic benefits of enhancing TNF-α levels. *See Exhibit 1, paragraphs 6-7.* While Applicants realize that actions taken by the PTO in other patent applications are not binding on the PTO with respect to the present application, Applicants note that numerous patents issued prior to Applicants' earliest priority date relate to the therapeutic benefits of enhancing TNF-α levels, indicating that prior to Applicants' earliest priority date the PTO found that inventions relating to the enhancement of TNF-α levels met the requirements of 35 U.S.C. §101. *Id. at paragraph 8.* As attested in paragraph 9 of Exhibit 1, the claimed nucleic acids encode polypeptides that in turn can be used to treat the conditions known to be ameliorated by increasing TNF-α levels.

Furthermore, as attested in the accompanying Declaration, it also was known prior to Applicants' earliest priority date that there are conditions in which it is beneficial to lower the levels of TNF-α. These conditions include rheumatoid arthritis and Crohn's disease. References published prior to Applicants' earliest priority date described the therapeutic benefits of decreasing TNF-α levels. *Id. at paragraph 10.* In addition, while Applicants realize that actions taken by the PTO in other patent applications are not binding on the PTO with respect to the present application, Applicants note that numerous patents issued prior to Applicants' earliest

priority date relate to the therapeutic benefits of decreasing TNF-α levels, indicating that prior to Applicants' earliest priority date the PTO found that inventions relating to decreasing TNF-α levels met the requirements of 35 U.S.C. §101. *Id. at paragraph 11.*

As described in Paragraphs [0361]-[0390] of the specification, the claimed nucleic acids encode polypeptides that can be utilized to generate antibodies which neutralize the activity of the polypeptide. Pharmaceutical compositions comprising the antibodies can be prepared as described in Paragraphs [0400]-[0409] and Example 10 of the specification. As attested in paragraph 12 of Exhibit 1, such antibodies can be used to reduce the activity of the PRO1356 polypeptide, thereby lowering TNF-α levels and achieving a therapeutic benefit.

Applicants have shown that contrary to the PTO's assertions, numerous references and patents were available at the time the instant application was filed which taught the benefits of regulating TNF-α release. Thus, Applicants submit that one of skill in the art would recognize the regulation of TNF-α release as a substantial utility.

Finally, Applicants turn to the PTO's argument that even though the PRO1356 polypeptide might have therapeutic benefit, the specification does not disclose "how it can be administered without the undesirable non-tumor cytotoxic activity outweighing the benefits of anti-tumor effects, how the side effects such as inflammation can be handled, and finally, how the leap can be made from release of TNF-α from blood to having a particular therapeutic benefit." Office Action at 3. There is no requirement to demonstrate therapeutic safety of a claimed compound in order to establish utility. In fact, it is well-established that it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness of a compound. MPEP 2107.03V; *see also In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981). Accordingly, a utility rejection cannot be premised on the fact that a specification does not disclose "how it can be administered without the undesirable ... side effects."

Specific Utility

Applicants next address the PTO's assertions the claimed nucleic acids lack a specific asserted utility. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of stimulation of TNF-α in blood by PRO1356, along with the declaration and references discussed above, provide a specific utility for the claimed nucleic acids encoding the PRO1356 polypeptide.

As discussed above, there are significant, reliable and reproducible data which show that the PRO1356 polypeptide stimulated the release of at least 50-fold more TNF-α than compared to the control. The Declaration of Dr. Godowski discusses several references which associate TNF-α with the treatment of diseases. Use of the claimed nucleic acids to generate polypeptides that regulate the stimulation of TNF-α release is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial and specific asserted utility: (1) the PTO states that the data in the specification demonstrating that PRO1356 stimulates the release of TNF-α in blood is not sufficient; (2) the PTO states that stimulation of TNF-α release in the bloodstream would not provide a utility; and (3) the PTO states that the specification does not provide guidance on administration of the PRO1356 polypeptide encoded by the claimed nucleic acids without undesirable side effects. Applicants have addressed each of these arguments in turn.

First, the PTO's position that the specification must demonstrate the statistical significance of experimental results in order to establish an asserted utility finds no basis under the utility requirement. Despite the PTO's position, Applicants have provided the Declaration of Paul Godowski stating that the data in Example 17 are real and significant. This declaration also indicates that given the at least fifty-fold increase in TNF-α levels, the disclosed polypeptides and claimed nucleic acids encoding those polypeptides have utility as therapeutic tools.

Second, a compound identified as having a pharmacological activity is recognized as meeting the utility requirement. Further, the Declaration and accompanying references demonstrate that it is well-established in the art that there are several conditions in which regulation of TNF-α release is beneficial. The PTO has not offered any substantial reasoning or evidence to the contrary.

Third, it is improper to premise a finding of utility on the condition that the claimed subject matter have demonstrated therapeutic safety.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the encoded PRO1356 polypeptide stimulates TNF-α release in blood. This is not a general utility that would apply to the broad class of nucleic acids.

Given the totality of the evidence provided, Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO1356 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections Under 35 U.S.C. §112 – Enablement

Claims 1-20 were rejected under 35 U.S.C. §112 on the assertion that because the claimed invention lacks utility, one skilled in the art would not know how to use the invention. Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-6, 9, 10 and 14-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require

that the claimed nucleic acids or encoded polypeptides possess any particular biological activity, particular conserved structure, or other disclosed distinguishing feature, the claims fail the written description requirement. The PTO states that the claims are drawn to a genus of nucleic acids that is defined only by sequence identity. The PTO also states that the term "extracellular domain" is not described in the specification. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience.

Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to a nucleic acid sequence encoding the polypeptide of SEQ ID NO:80; a nucleic acid sequence encoding the polypeptide of SEQ ID NO:80, lacking its associated signal peptide; a nucleic acid sequence encoding particular portions of SEQ ID NO:80; the nucleic acid sequence of SEQ ID NO:79, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:79, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203241, with the functional recitation as amended: "wherein said isolated nucleic acid encodes a protein that stimulates the release of TNF-α in blood." or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO:79" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO:79, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:79, the full-length coding sequence of the cDNA deposited under ATCC accession number 203241, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they

hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument that the claimed nucleic acids do not possess any particular conserved structure, or other disclosed distinguishing feature. The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO: 79, such that they hybridize to SEQ ID NO:79 or the related sequences under the specified high stringency conditions recited in the claims.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:79 with the functional recitation "wherein said isolated nucleic acid encodes a protein that stimulates the release of TNF-α in blood" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic

activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must encode a protein with the recited biological function. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the encoded protein stimulates the release of TNF-α in blood. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must encode a protein with the recited biological activity.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did nõt actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 2-7.

Regarding the rejection of the claims for reciting "extracellular domain," the claims are amended to no longer recite this term. Thus, this basis for rejection of the claims is now moot.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:79, by specifying the high stringency conditions under which hybridization occurs, and by describing the TNF-α assay in Example 17, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Applicants also have amended the claims to no longer recite "extracellular domain." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has also rejected Claims 1-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the recitation of "extracellular domain" because allegedly no extracellular domain was described. The PTO also objects to recitation of "a nucleic acid that hybridizes" because the intended hybridization conditions are allegedly unknown.

As discussed above, Applicants have amended the claims to no longer recite "extracellular domain." Claim 14 has been amended to specify the conditions under which hybridization occurs. Claim 15 has been canceled. In light of these amendments, Applicants request that the PTO withdraw the indefiniteness rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b) – Anticipation

Claims 1-3, 14, and 16-20 are rejected as being anticipated under 35 U.S.C. § 102(b) by GenBank Accession AL158821 (hereinafter AL158821), WO 00/18915 (Yue *et al.*, published April 6, 2000), and WO 99/25825 (Bougueleret *et al.*, published May 27, 1999). These references all allegedly disclose a nucleotide sequence encoding a polypeptide sequence 100% identical to SEQ ID NO:80 of the present application.

Applicants respectfully traverse.

The sequences of SEQ ID NOs: 79 and 80 and homologies of these sequences to known genes and gene families were first disclosed in US Provisional Application 60/099792 filed 9/10/1998 as SEQ ID NOs: 1 and 2, in Figures 1 and 2. The data in Example 17 (Identification of PRO Polypeptides That Stimulate TNF-α Release In Human Blood (Assay 128)), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 92, line 25, through page 93, line 1.

AL158821

Applicants submit that AL158821 cannot anticipate the claimed nucleic acids because AL158821 is not prior art under 35 U.S.C. § 102(b). To anticipate under 35 U.S.C. § 102(b), the claimed subject matter must be described in a printed publication more than one year prior to the priority date of the application for patent. The date listed at the top of AL158821 is February 8, 2002. Applicants presume this is the date of publication asserted by the PTO. The PTO has

recognized the filing date of the subject application as May 8, 2002. Thus, even absent recognition of any of Applicants' priority documents, AL158821 was not published more than one year prior to the filing of this application. Accordingly, AL158821 is not prior art under35 U.S.C. § 102(b).

Yue

Applicants submit that Yue (published April 6, 2000), cannot anticipate the claimed nucleic acids because Yue is not prior art under 35 U.S.C. § 102(b). To anticipate under 35 U.S.C. § 102(b), the claimed subject matter must be described in a printed publication more than one year prior to the priority date of the application for patent. Yue was not published more than one year prior to the priority date of either priority documents US Provisional Application 60/099792 (filed 9/10/1998) or PCT Application PCT/US00/23328 (filed 8/24/200). Accordingly, Yue is not prior art under35 U.S.C. § 102(b).

Bougueleret

Applicants submit that Bougeleret (published May 27, 1999), cannot anticipate the claimed nucleic acids because Bougeleret is not prior art under 35 U.S.C. § 102(b). Bougeleret was not published more than one year prior to the filing date of priority document US Provisional Application 60/099792 (filed 9/10/1998). Accordingly, Bougeleret is not prior art under 35 U.S.C. § 102(b).

Even if the PTO disallows Applicants' earliest priority date, Applicants submit that Bougueleret is not prior art because Applicants were in possession of at least as much of the claimed invention as is set forth in Bougueleret. The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound

called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention."

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (*Id.* at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference, an applicant need only show prior possession of that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively remove that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority to a patent application that predates the cited reference. Applicants demonstrated, by means of the disclosure in their provisional application filed September 10,

1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO:80 of the present application, as disclosed in the Bougeleret reference published May 27, 1999, i.e., SEQ ID NO:186 of Bougeleret. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102(b) over Bougeleret be removed.

CONCLUSION

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 5, 2005

By: _____

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DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, Christopher J. Grimaldi and Colin K. Watanabe.

Applicants request that these inventors be deleted, as their inventions are no longer being claimed in the present application as a result of prosecution.